

**The Flavor and Fragrance High Production Volume Consortia
(FFHPVC)**

**1620 I Street, N.W.
Suite 925
Washington D.C. 20006
Tel. (202)-331-2325 Fax (202)-463-8998**

March 27, 2002

Christie Todd Whitman, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Ms. Whitman:

On behalf of the member companies of the Terpene Consortium, the Flavor and Fragrance High Production Volume Consortia is pleased to submit the Test Plan and Robust Summaries for the chemical category designated the "Ionone Derivatives" to the HPV Challenge Program, AR-201. The Terpene Consortium has chosen not to belong to the HPV Tracker System for submission of test plans and robust summaries. We are therefore submitting the test plan and accompanying robust summaries directly to EPA to make available to the public. This submission includes one electronic copy in pdf. format. A hard copy of this submission is available upon request. The EPA registration number for the Terpene Consortium is

Please feel free to contact me with any questions or comments you might have concerning the submission at tadams@therobertsgroup.net, tadams@chemintox.com or 202-331-2325.

Sincerely,
Timothy Adams, Ph.D.
Technical Contact Person for FFHPVC

AR201-13660A

The Flavor And Fragrance High Production Volume Consortia

The Terpene Consortium

Test Plan For Ionone Derivatives

Methyl ionone (mixture of isomers)

CAS No. 1335-46-2

alpha-iso-Methylionone

CAS No. 127-51-5

FFHPVC Terpene Consortium Registration Number

**Submitted to the EPA under the HPV Challenge Program by:
The Flavor and Fragrance High Production Volume Chemical Consortia
1620 I Street, NW, Suite 925
Washington, DC 20006
Phone: 202-331-2325
Fax: 202-463-8998**

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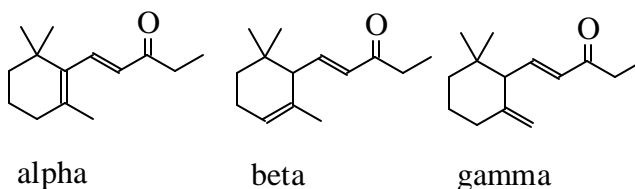
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The HPV Challenge Test Plan for Ionone Derivatives

1 Identity of Substances



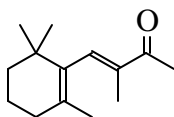
Methyl ionone (mixture of isomers)



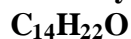
Synonyms:

1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl) (*alpha* methylionone isomer)
1-Penten-3-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl) (*beta* methylionone isomer)
1-Penten-3-one, 1-(6,6-methyl-2-methylenecyclohex-1-yl) (*gamma* methylionone isomer)
3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)- (*alpha-iso*-methylionone isomer)
3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- (*beta-iso*-methylionone isomer)
3-Buten-2-one, 3-methyl-4-(6,6-dimethyl-2-methylenecyclohex-1-yl)- (*gamma-iso*-methylionone isomer)

CAS No. 1335-46-2



alpha-iso-Methylionone



Synonyms:

3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-
Isoraldeine
alpha-iso-Methylionone

CAS No. 127-51-5

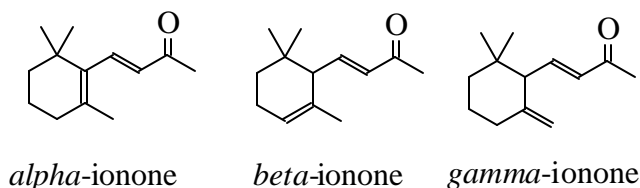
2 Category Analysis

2.1 Introduction

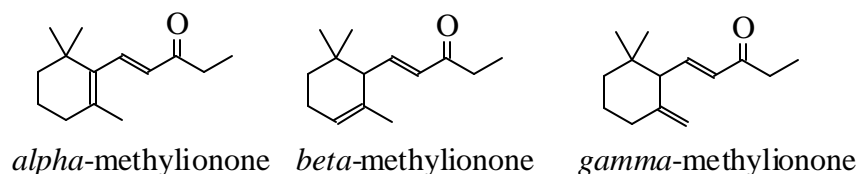
In October of 1999, members of the United States flavor and fragrance industries as well as other manufacturers that produce source materials used in flavors and fragrances formed consortia of companies in order to participate in the Chemical Right-to-Know Program. Members of these consortia committed to assuring the human and environmental safety of substances used in flavor and fragrance products. The consortia are organized as the Flavor and Fragrance High Production Volume Consortia (FFHPVC). The Terpene Consortium, as a member of the Flavor and Fragrance High Production Volume Consortia serves as an industry consortium to coordinate testing activities for terpenoid substances under the Chemical Right-to-Know Program. Twenty-one (21) companies are current members of The Terpene Consortium. The Terpene Consortium and its member companies are committed to assembling and reviewing available test data, developing and providing test plans for each of the sponsored chemicals, and, where needed, conducting additional testing. The test plan, category analysis, and robust summaries presented represent the first phase of the Consortiums commitment to the Chemical Right-to-Know Program.

2.2 Background Information

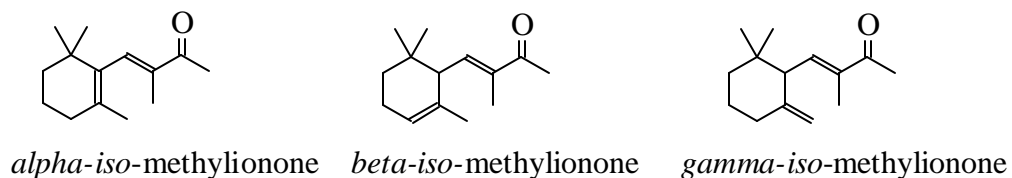
The chemical category designated “Ionone Derivatives” includes two substances that are in reality a mixture of ionone isomers. Ionone, the parent terpene, occurs in nature as one of three isomers (*alpha*, *beta*, and *gamma*). Chemically, ionone is 4-(2,6,6-trimethylcyclohexen-1-yl)-2-buten-3-one. The three isomers differ only in the presence of a double bond at the 1, 2, or 2(exocyclic) position of the cyclohexane ring.



Methylionone exhibiting the same double bond isomers as ionone contains an additional methyl group at the terminal position (4-position) of the butanone side chain.



iso-Methylionone exhibiting the same double bond isomers as ionone contains an additional methyl group at the 2-position of the butenone side chain.



Ionones, methylionones and *iso*-methylionones are used as both fragrances and in food flavorings. *alpha*-Ionone and *beta*-ionone are a class of cyclic terpenoids occurring in essential oils exhibiting a sweet floral scent reminiscent of violets. Methylionones and *iso*-methylionone exhibit aromas associated with orris or violets.

2.3 Regulatory Status

A group of 21 ionone derivatives (Table 1) including the above substances have been reviewed by the Joint Expert Committee on Food Additives (JECFA) [JECFA, 1999] for use as flavoring substances in food. As part of its responsibility for the World Health Organization, JECFA maintains an ongoing program of review of the safety of flavor agents used as food additives (WHO Technical Series Nos. 38, 40, 42, 44). In 1999, these 21 ionone derivatives were recognized as safe under current conditions of use as flavoring substances added to food. These ionone derivatives are also recognized as Generally Recognized as Safe (GRAS) for their intended use in food by the United States Food and Drug Administration under the Code of Federal Regulations (CFR 172.515)

Table 1. *alpha*- and *beta*-ionone and Structurally Related Substances Used as Flavoring Substances

SUBSTANCES	FEMA No.	CAS No.
4-[(2,6,6)-Trimethyl-cyclohex-1-enyl] but-2-en-4-one (<i>beta</i> -Damascone)	3243	23726-92-3
<i>alpha</i> -Damascone	3659	43052-87-5
<i>delta</i> -Damascone	3622	57378-68-4
4-(2,6,6-Trimethylcyclohexa-1,3-dienyl)but-2-en-4-one	3420	23696-85-7
1,4-Dimethyl-4-acetyl-1-cyclohexene	3449	43219-68-7
<i>alpha</i> -ionone	2594	127-41-3
<i>beta</i> -ionone	2595	14901-07-6
<i>gamma</i> -ionone	3175	79-76-5
<i>alpha</i> -ionol	3624	25312-34-9
<i>beta</i> -ionol	3625	22029-76-1
Dihydro- <i>alpha</i> -ionone	3628	31499-72-6
Dihydro- <i>beta</i> -ionone	3626	17283-81-7
Dihydro- <i>beta</i> -ionol	3627	3293-47-8
Dehydrodihydroionone	3447	20483-36-7
Dehydrodihydroionol	3446	57069-86-0
Methyl- <i>alpha</i> -ionone	2711	127-42-4
Methyl- <i>beta</i> -ionone	2712	127-43-5
Methyl- <i>delta</i> -ionone	2713	7748-98-7
Allyl- <i>alpha</i> -ionone	2033	79-78-7
<i>alpha</i> -Irone	2597	79-69-6
<i>alpha</i> -iso-Methylionone	2714	127-51-5

2.4 Natural Occurrence

In plants, monoterpene ketones, such as *beta*-ionone, are formed by the biochemical oxidative cleavage of *beta*-carotene. The occurrence of *beta*-ionone in carrots arises from oxidation and cleavage of the 9'-10' double bond of *beta*-carotene. *beta*-ionone is also present as a minor metabolite in the animal metabolism of *beta*-carotene. In animals, *beta*-carotene is oxidized by carotenoid dioxygenase(s) and cleaved at the 15'-15' (central) double bond to yield two molecules of vitamin A (retinal) [Simpson and Chichester, 1981] which may be subsequently cleaved at the 9'-10' double bond to yield *beta*-ionone and 10'-apo-*beta*-carotenals. The presence of 10'-apo-*beta*-carotenal in rat liver following oral administration of *beta*-carotene is evidence that oxidative cleavage of the 9'-10' double bond occurs in animals [Sharma *et al.*, 1977].

Ionone derivatives occur mainly in plants containing *beta*-carotene. They have been detected in a variety of foods including raspberries, carrots, roasted almonds, fruits and herbs [CIVO-TNO, 1999]. Eleven of the substances in the group of 21 have been reported to occur naturally in foods [CIVO-TNO, 1999]. Quantitative natural occurrence data and consumption ratios have been reported for 7 substances in the group and demonstrate that their consumption occurs predominantly from traditional foods (i.e., consumption ratio greater than 1) [Stofberg and Kirschman, 1985; Stofberg and Grundschober, 1987].

2.5 Structural Classification

The chemical category designated ionone derivatives includes *alpha*-iso-methylionone and a mixture of the *alpha*, *beta*, and *gamma* isomers of methylionone. Chemically, the only structural difference between *alpha*-iso-methylionone and the methylionone mixture is that *alpha*-iso-methylionone contains an additional methyl group at the 2-position of 4-(2,6,6-trimethylcyclohexen-1-yl)-2-buten-3-one (*alpha*-ionone) while methylionone contains an additional methyl group at the 4-position of 4-(2,6,6-trimethylcyclohexen-1-yl)-2-buten-3-one (*alpha*-ionone).

2.6 Industrial and Biogenic Production

2.6.1 Industrial Production

Methylionone derivatives are produced predominantly by the base catalyzed condensation of citral and methyl ethyl ketone. The reaction yields a mixture of *n*- and *iso*-pseudoionone, each of which may occur as four *cis-trans* isomers. The ratio of *n*- to *iso*-isomers depends on the condensation catalyst and reaction conditions. The normal (*n*-) isomers are favored when common alkaline catalysts are used. *Iso*-isomers are favored when strong alkaline catalysts such as quaternary ammonium bases are used [Beets and van Essen, 1959]. The preparation of the important fragrance *alpha-iso*-methylionone can be obtained in excellent yield from the reaction of dehydrolinalool with the enol ether of methyl ethyl ketone and methanol [Hoffman-LaRoche, 1961].

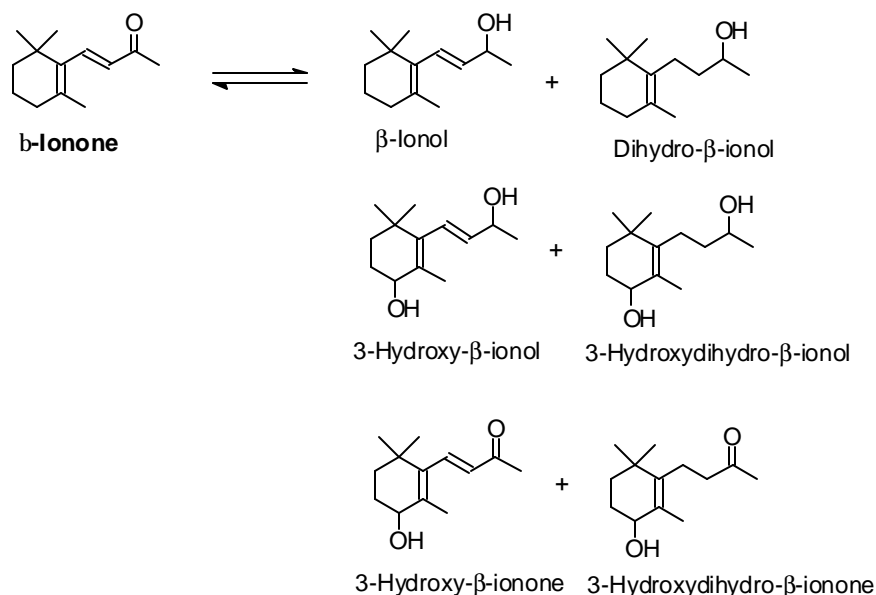
Cyclization of the open chain methylpseudoionones is accomplished with mineral acid (*e.g.*, sulfuric or phosphoric acid) and Lewis acid (*e.g.*, boron trifluoride etherate) catalysts. The ratio of *alpha*, *beta*, and *gamma* isomers of *iso*-methylionone and *n*-methylionone depends on the catalyst used and fluctuates from one manufacturer to another.

2.6.2 Chemical Reactivity and Metabolism

Orally administered ionones are absorbed and metabolized in mammals by allylic hydroxylation of the ring followed by oxidation of the hydroxyl group to 3-oxo derivatives. Reduction of the ketone function to the corresponding secondary alcohol also occurs. Combinations of these detoxication reactions result in the formation of multiple polar metabolites, which are excreted in the urine unchanged or conjugated with glucuronic acid (see Figure 1).

A total of 170 g *alpha*-ionone was fed to 2 rabbits over an unspecified period. Analysis of collected urine revealed a hydroxylated derivative of *alpha*-ionone [Prelog and Wursch, 1951] formed from allylic ring oxidation.

FIGURE 1. METABOLISM OF *BETA*-IONONE IN RABBITS



A 3 kg male rabbit was orally administered a total of 23 g *beta*-ionone for 7 days (approx. 1000 mg/kg bw/day). Urine was collected daily and for 4 days after the final dose. Allylic ring oxidation and ketone reduction yielded 3-oxo-ionone, 3-oxo-*beta*-ionol, dihydro-3-oxo-*beta*-ionol, and 3-hydroxy-*beta*-ionol, which were detected in the urine. Unchanged *beta*-ionone and the glucuronic acid conjugates of 3-oxo- *beta*-ionol and dihydro-3-oxo-*beta*-ionol were also detected [Ide and Toki, 1970] (see Figure 1). Two rabbits received a total of 100 g *beta*-ionone over 18 days via esophageal tube. Metabolites identified in urine, which was collected throughout the treatment period, included 3-hydroxy-*beta*-ionone, 3-oxo-*beta*-ionol, and 3-hydroxy-*beta*-ionone¹. A hydroxyketone thought to be either 3-oxo-*beta*-ionol or 3-hydroxy-*beta*-ionone was also recovered [Fujii *et al.*, 1972].

The exocyclic dihydro metabolites of *beta*-ionone and *beta*-ionol have also been detected in rabbits. *beta*-Ionone in 20% alcohol was orally administered to 3 rabbits in doses of 2000 to 5000 mg/day for 2 weeks. Analysis of urine revealed *beta*-ionol, *beta*-ionone,

¹ Urinary metabolites are identified here using IUPAC nomenclature. Metabolites are reported in the reference using a different naming system.

dihydro-*beta*-ionol, 3-hydroxy-*beta*-ionol, 3-hydroxy-dihydro-*beta*-ionol, 3-hydroxy-*beta*-ionone, and 3-hydroxy-dihydro-*beta*-ionone¹ [Bielig and Hayasida, 1940] (see Figure 1). Two dogs fed a total of 100 g *beta*-ionone over 18 days excreted 3-oxo-*beta*-ionone and 3-hydroxy-*beta*-ionol in the urine [Prelog and Meier, 1950].

beta-Ionone has been found to induce biphenyl 4-hydroxylase, glucuronyl transferase, 4-nitrobenzoate reductase, and cytochrome P-450 in rats following 3-day administration via either intraperitoneal injection or food [Parke and Rahman, 1969].

The metabolism of ionones is expected to be similar in humans. This is supported by human metabolism studies of retinoids and carotenoids such as *cis*-13-retinoic acid (i.e., isotretinoin) and *beta*-carotene, respectively, which possess ionone fragments. The primary blood and biliary metabolites following oral administration of isotretinoin to humans include the glucuronic acid conjugates of isotretinoin [Kraft *et al.*, 1991] and the allylic oxidation product [Vane *et al.*, 1990; Kraft *et al.*, 1991]. Both metabolites were observed in the blood and bile of cynomolgous monkeys provided in isotretinoin via the oral route [Kraft *et al.*, 1991]. Allylic hydroxylation of the methyl ring substituent and subsequent conjugation with glucuronic acid also occurs in humans [Vane *et al.*, 1990].

3 Test Plan

3.1 Chemical and Physical Properties

3.1.1 Melting Point

The two substances in this chemical category are liquids at ambient temperature. Calculated value for *alpha-iso*-methylionone and methylionone (mixture of isomers) are 45.26 °C and 59.38 °C, respectively (mean value) [MPBPWIN EPI Suite, 2000].

3.1.2 Boiling Point

Literature values are available for *alpha-iso*-methylionone and methylionone (mixture of isomers). The Fragrance Materials Association (FMA) has reported that *alpha-iso*-methylionone and methylionone (mixture of isomers) both exhibit a boiling point of 238 °C @ 760 mm [FMA]. The experimental boiling point reported for *alpha-iso*-methylionone is 266.2 °C @ 749 mm (1013 Pa), 162.2 °C @ 39 mm Hg (53.3.Pa), and 126.5 °C @ 10 mm Hg (13.3 Pa) [Hoffmann-LaRoche, Inc., 2000]. The calculated values [MPBPWIN EPI Suite, 2000] for *alpha-iso*-methylionone and methylionone (mixture of isomers) of 271.6 °C and 274.6 °C (adapted Brown and Stein Method) are in good agreement with measured values given that boiling points were measured for mixtures of isomers.

3.1.3 Vapor Pressure

The calculated vapor pressure value [MPBPWIN EPI Suite, 2000] is in the range from 0.00146-0.00150 kPa (0.0124 to 0.0127 mm Hg) (modified Grain method) for *alpha-iso*-methylionone based on an experimental boiling point of 266.2 °C [Hoffmann-LaRoche, 2000]. The calculated vapor pressure value [MPBPWIN EPI Suite, 2000] is estimated to be 0.00124 kPa (0.0093 mm Hg) (modified Grain method) for methylionone mixture based on the same experimental boiling point [Hoffmann-LaRoche, 2000]. These

calculated values are in good agreement with vapor pressure values reported by the Fragrance Materials Association. The calculated vapor pressures for *alpha-iso-methylionone* and methylionone mixture are 0.006 and 0.005 mm Hg, respectively [FMA, 2000]. The range of vapor pressure at ambient temperature is fairly narrow. The vapor pressure for ionone derivatives in this category are in the range from 0.009 to 0.013 mm Hg. Based on the close agreement among these values, no further testing is recommended.

3.1.4 n-Octanol/Water Partition Coefficient

The measured log Kow values for methyl ionone mixture containing 87.8% *alpha-iso-methylionone* is 4.6 using an OECD 117 test protocol [Rudio, 1994a]. This is in good agreement with the measured log Kow of 4.1 for lower molecular weight ionone *beta-ionone* using the same OECD 117 protocol performed at the same laboratory [Rudio, 1994b]. The measured log Kow value for *alpha-iso-methylionone* is also in good agreement with the calculated values of log Kow values of 4.84 for both members of this chemical category. [KOWWIN EPI Suite, 2000]. The narrow range and the close agreements with the one measured value and the calculated values indicate consistency and imply reliability. Based on the mutual agreement of these values, no further partition coefficient studies are recommended.

3.1.5 Water Solubility

The reported water solubility for *alpha-iso-methylionone* is 16 mg/L at 20 °C following an OECD 105 protocol for determination of water solubility [Schlienger, 1992b]. A measured value of 90 mg/L was reported for *gamma-methylionone* but the temperature was specified [BBA, 1990]. The calculated value [WSKOWIN EPI Suite, 2000] for *alpha-iso-methylionone* or methylionone mixture is 4.8 mg/L at 25 °C. The solubility of the two members of this chemical category at 20 °C is expected to be in the range from approximately 15 mg/L. No further solubility studies are recommended.

3.1.6 New Testing Required

None.

3.2 Environmental Fate and Pathways

3.2.1 Photodegradation

The calculated photodegradation half-lives [AOPWIN EPI Suite, 2000] for the reaction of structurally defined substance *alpha-iso*-methylionone with hydroxyl (OH) radicals or ozone (O₃) is 0.75 or 0.5 hours, respectively. These calculations are based on measured rate constants for *alpha-iso*-methylionone, but would expected to be the same for the methylionone mixture based on the presence of the *alpha-iso*-methyl isomer in the mixture and the close structural relationship among all members of this category.

3.2.2 Stability In Water

No hydrolysis is possible for any of the materials in this group. All are expected to be very stable in aqueous solution.

3.2.3 Biodegradation

Five GLP experimental studies evaluating biodegradability are available for this group of substances using standard OECD protocols. Three studies on methylionone isomers showed ready biodegradability. The first, which followed a MITI OECD 301C protocol, reported 70.5% biodegradation at 28 days with 10% biodegradation reached within 5 days [Calame and Ronchi, 1990]. The second study on methylionone, which followed a Method F protocol and evaluated ready biodegradability, reported 99.1% biodegradation at 31 days [Stickley, 1990]. In the third test using a respirometric method, methylionone was reported to be 80% degraded within 28 days [Givaudan-Roure, 1991].

Two biodegradability tests have been performed for *alpha-iso*-methylionone. In the first test using a Modified MITI OECD 302C protocol, *alpha-iso*-methylionone exhibited primary inherent biodegradability of 63.4% after 56 days and was slightly toxic to microorganisms [Schlienger, 1992a]. In a later test using an OECD 301B protocol, *alpha-iso*-methylionone was considered as inherently biodegradable under modified ready test conditions (61.8% after 28 days) [King, 1992]. Given the close structural relationship between *alpha-iso*-methylionone and methylionone and the fact that the methylionone mixture contains significant amounts of the *alpha-iso*-methyl isomer, it is unlikely the two substances should exhibit any significant difference in biodegradability according to standardized protocols. The results of the five studies support that conclusion. Therefore, it is likely that members of this chemical category will exhibit ready biodegradability.

3.2.4 Fugacity

Transport and distribution in the environment were modeled using Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11 [Trent University, 1999]. The principal input parameters into the model are molecular weight, melting point, vapor pressure, water solubility, and log Kow. Where measured values were available, these were used, but where they were not, calculated data from the EPIWIN series of programs were used. Given the similarity of structure and physical properties of the substances in this category, they would be predicted to exhibit similar distribution in the environment. The value of these calculations must be evaluated in the context that the substances in this chemical category are products of plant biosynthesis and are, therefore, ubiquitous in the environment. Also, the models fail to account for the known chemical reactivity of these substances.

3.2.5 New Testing Required

None.

3.3 Ecotoxicity

3.3.1 Acute Toxicity to Fish

The two substances, *alpha-iso-methylionone* and *beta-ionone* have measured fish acute toxicity data [Schlienger, 1992b; Grothe, 1989]. The 96-hour LC50 of 10.9 mg/L for *alpha-iso-methylionone* in rainbow trout (*Oncorhynchus mykiss*) agree with limit data for *beta-ionone* in the same species [Grothe, 1989]. The LCO value of 5.0 mg/L [Grothe, 1989] for *beta-ionone* indicates that the acute LC50 for rainbow trout is in the range of 10 mg/L. The calculated LC50 of less than 1 mg/L for *alpha-iso-methylionone* is estimated as a neutral organic and 2-3 mg/L estimated as vinyl/allyl ketone demonstrates the conservative nature of the ECOSAR model [ECOSAR EPI Suite, 2000]. Based on the experimental data, the two ionone derivatives exhibit low acute toxicity to fish.

3.3.2 Acute Toxicity to Aquatic Invertebrates

The principal substance in this group, *alpha-iso-methylionone* exhibits a 48-hour LC50 of 0.6 mg/L in *Daphnia magna* calculated both as a neutral organic and a vinyl/allylketone [ECOSAR EPI Suite, 2000]. In order to validate the model, it is recommended that an acute LC50 in *Daphnia magna* should be determined for *alpha-iso-methylionone* using an OECD 202 guideline.

3.3.3 Acute Toxicity to Aquatic Plants

The principal substance in this group, *alpha-iso-methylionone* exhibits a calculated 48-hour EC50 of 0.332 or 0.266 mg/L in *Daphnia magna* calculated both as a neutral organic and a vinyl/allylketone [ECOSAR EPI Suite, 2000]. In order to validate the model, it is recommended that an acute EC50 in algae should be determined for *alpha-iso-methylionone* using an OECD 201 guideline.

3.3.4 New Testing Required

- An acute LC50 for *alpha-iso-methylionone* is recommended in *Daphnia magna* using OECD 202 Guideline.
- An acute EC50 for *alpha-iso-methylionone* is recommended in algae using OECD 201 Guideline.

3.4 Human Health Toxicity

3.4.1 Acute Toxicity

Rat oral LD50 values available for *alpha-ionone*, *alpha-iso-methylionone*, methylionone (mixture of isomers), and *gamma-ionone* indicate these materials to be very low in oral acute toxicity. The LD50 values of all four substances are greater than 5000 mg/kg bw [Moreno, 1973a, 1973b, 1977a, 1977b]. Mouse oral LD50 values are also greater than 5000 mg/kg bw for *alpha-ionone*, *alpha-iso-methylionone*, and methyl ionone (mixture of isomers). The mouse oral LD50s are reported to be 6650 mg/kg bw for *alpha-ionone*, 5331 mg/kg bw for methylionone, and 8714 for *alpha-isomethylionone* [Hoffman LaRoche, 1967]. The acute dermal LD50s reported for *alpha-iso-methylionone*, methylionone (mixture of isomers), and *gamma-ionone* are all greater than 5000 mg/kg bw [Moreno, 1973a, 1977a, 1977b]. Based on these results the acute oral and dermal toxicities of ionone derivatives is concluded to be very low.

3.4.2 Genetic Toxicity

3.4.2.1 In vitro Genotoxicity

In vitro genotoxicity assays available for various ionone and methyl ionone isomers demonstrate that these substances have a little, if any, genotoxic potential. *beta-Ionone* exhibited no mutagenic activity in established strains of *Salmonella typhimurium* (strains TA98, TA100, TA1535 and TA1537) at concentrations up to approximately 180 µg/plate

with and without metabolic activation [Mortlemans *et al.*, 1986; Florin *et al.*, 1980]. Two methylionone isomers, *alpha*- and *delta*-methylionone exhibited no mutagenic activity in *Salmonella typhimurium* TA100, TA1535, TA1537, TA1538 and TA1598 with and without S-9 activation, at concentrations up to approximately 3600 µg/plate [Wild *et al.*, 1983]. No mutagenic activity was observed in *Salmonella typhimurium* strains TA98 and TA100 when treated with *alpha*-ionone at concentrations up to approximately 50 µg/plate with and without metabolic activation [Kasamaki *et al.*, 1982]. In recent study [Wagner and Caruthers, 1999], there is no evidence of mutagenicity or precipitation at concentrations up to and including 5000 ug/plate when methylionone was incubated with *Salmonella typhimurium* TA100, TA98, TA1535, and TA1537. Toxicity was observed at concentrations of 1800 ug/plate with TA100 and 1800 ug/plate with TA1537. In a chromosome aberration test using Chinese hamster cells, line B241, *alpha*-ionone was positive at a concentration of 25 mM (5150 ug/ml). However, this study must be interpreted with caution since the investigators made no attempt to monitor cytotoxicity in CHO cells [Kasamaki *et al.*, 1982].

3.4.2.2 In vivo Genotoxicity

No increase in the frequency of sex-linked recessive mutations occurred when *Drosophila melanogaster* were maintained on 20 mM solutions of *alpha*-methylionone [Wild *et al.*, 1983].

In a clastogenicity assay, groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 333, 666, or 1,000 mg/kg bw of *alpha*-methylionone [Wild *et al.*, 1983]. At 30 hours, the mice were sacrificed and bone marrow smears were prepared using the staining method of Schmid (1976). There was no evidence of micronucleated polychromatic erythrocytes for treated or control groups (mean number of micronucleated PE/1000 NCE at 0, 825, 1444 or 2063 mg/kg bw was 1.7, 1.0, 0.7, or 1.9, respectively).

Based on the results of this *in vivo* genotoxicity assays and the lack of any evidence of genotoxicity for numerous *in vitro* assays with and without metabolic activation, it is

unlikely that any of these materials would exhibit a significant genotoxic potential *in vivo*. No additional *in vitro* and *in vivo* assays are requested for this chemical category.

3.5 Repeat Dose Toxicity

Ninety (90) day dietary studies have been performed with *alpha*-iso-methylionone *alpha*-ionone, *beta*-ionone in both sexes of rats [Oser *et al.*, 1965]. Groups of 15 FDRL rats (per sex per dose) were housed individually and maintained on a diet containing the test article diluted in cotton-seed oil (2%), a concentration sufficient to provide an average daily intake of 3.55 or 4.10 mg/kg bw of *alpha*-iso-methylionone for males and females, respectively. Animals were housed individually. Weekly measurement of body weights and food and water intake revealed no significant differences between test and control animals. Hematological examination and blood chemical determinations performed on 8 rats at week 6 and on all rats at week 12 showed normal values. Measurement of liver and kidney weights at necropsy showed no differences in absolute or relative organ weights between test and control groups. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis. Based on gross and histopathological examination, there were no alterations that could be associated with administration of *alpha*-iso-methylionone.

In the two other studies using the same protocol, no evidence of toxicity was reported when groups of male and female FDRL rats were maintained on diets calculated to result in an average daily intake of 11.8 or 10.6 mg/kg bw of *alpha*-ionone or 11.6 or 11.4 mg/kg bw of *beta*-ionone, respectively, for 90 days, [Oser *et al.*, 1965].

In two other dietary studies, groups of Sprague-Dawley rats (15/sex/group) housed in groups of 3 were maintained on diets calculated to contain 10 or 100 mg/kg bw of *alpha*-ionone or *beta*-ionone for 90 days. Body weights and food and water intake were measured every 3rd or 4th day of the study. Hematological examination was performed on rats during weeks 6 and 13 of the study. Blood chemical determinations and urinalysis were performed on weeks 5 and 12. At necropsy, organ weights (brain, liver,

spleen, kidneys, caecum, adrenals and gonads (males)) were measured. Histopathological examination of a wide variety of tissues (adrenal, aorta, bladder, brain, caecum, colon, diaphragm, duodenum, epididymis, eye, harderian gland, heart, ileum, kidney, liver, lung, lymph nodes, mammary, muscle, esophagus, ovary, pancreas, pituitary, prostate, rectum, seminal vesicles, skin, spinal cord, spleen, stomach and testis) were performed for the controls and high dose groups. The liver of the low dose group was also subjected to histopathological examination.

In the *alpha*-ionone study, actual intake was determined to be 11 mg/kg bw for males and females at the 10 mg/kg bw target dose and 106-108 mg/kg bw at the 100 mg/kg bw target dose. Food intake of the high dose group of males and females were significantly lower than controls. A decrease in neutrophils and lymphocytes were reported in males at the high dose level at week 6 but not at week 13. At the high dose, lower alkaline phosphatase in males and lower glucose levels in females was reported. The relative kidney weights were statistically significantly greater in males at the high dose. Relative and absolute mean liver weights were statistically increased in males at the high dose. The only histological finding was desquamation of the thyroid in females only at the high dose. The NOAEL for *alpha*-ionone was reported to be 10 mg/kg [Gaunt *et al.*, 1983].

In the *beta*-ionone study, the actual intake of *beta*-ionone was determined to be 11 mg/kg bw for males and females at the 10 mg/kg bw target dose and 106-108 mg/kg bw at the 100 mg/kg bw target dose. Food intake of the high dose group of males and females were significantly lower than controls. A decrease in erythrocyte counts and hematocrit were reported in males at the high dose levels at week 6 but not at week 13. At the high dose, lower alkaline phosphatase in males and lower glucose levels in females was reported. Relative and absolute mean liver weights were statistically increased in males at the high dose. Relative brain, caecal, liver and kidney weights were statistically increased in females at the high dose level. The NOAEL for *beta*-ionone was reported to be 10 mg/kg [Gaunt *et al.*, 1983].

In a dermal 90-day study with one of the methylionone isomers (*gamma*-methylionone), a 1% *gamma*-methylionone solution in phenethyl alcohol at a dose of 10 mg/kg was

applied topically to the clipped backs of individually housed Sprague-Dawley rats (5/sex/group) daily for 90 days. A control group of 5 male and female rats received 1 ml/kg phenyl ethyl alcohol. Body weights were measured weekly. Hematological examination, clinical chemistry determinations and urinalysis were performed on all animals at termination. At necropsy, liver and kidney weights were measured and histopathological examination was made of the skin, kidneys, liver, sternal bone, and spinal cord. There was no evidence of toxicity induced by treatment with the *gamma* methyl ionone [Moreno, 1981].

Based on the results of dietary studies with *alpha-iso*-methylionone, *alpha*-ionone, and *beta*-ionone [Oser *et al.*, 1965; Gaunt *et al.*, 1983] and a dermal study with *gamma*-methylionone, it is concluded that none of the ionone derivatives exhibits any evidence of toxicity at dose levels up to and including 10 mg/kg bw/day.

3.5.1 Reproductive Toxicity

The effect of ionone (*alpha*- and *beta*-ionone) on the reproduction in 48 white rats was investigated. The females received 0.1 ml oil solution containing 2 mg ionone by gavage every other day for 8 months. Males were also given 2mg/day every other day for 8 months. The dose corresponds to a daily intake of approximately 8 to 10 mg/kg bw/day. Females were followed through 3 reproduction cycles. Females were monitored for number of pregnancies, average weight, number of born offspring, number of offspring born alive, weight at birth and after 7 and 21 days, and viability of offspring after each reproduction. Females received 24 mg before the first reproduction, 84 mg before the second, and 208 mg before the third reproduction. Offspring from the first reproduction (F1) were allowed to reach maturity. This F1 generation received 15 mg ionone prior to reproduction. The F1 generation was then monitored for the same parameters as for females above. Based on data collected from three reproductive cycles of female rats and on reproductive cycle of F1 offspring given 2 mg/day every other day (approximately 8-10 mg/kg bw per day) by gavage, there is no evidence of reproductive toxicity [Sporn *et al.*, 1965].

The lack of reproductive toxicity [Sporn *et al.*, 1965] is supported by observations made in two separate repeat dose studies [Oser *et al.*, 1965; Gaunt *et al.*, 1983] in which there was no evidence (organ weight, gross or histopathological) toxicity to reproductive organs (testis, seminal vesicles, ovaries) of rats maintained on diets of up to 100 mg/kg bw/day for 90 days. Therefore, it is concluded that none of the ionone derivatives discussed show any evidence of reproductive toxicity.

3.5.2 Developmental/Teratogenicity Toxicity

Groups of pregnant LAK:LVG(SYR) hamsters were given 0, 48, 240, or 480 mg/kg bw of *beta*-ionone dissolved in acetone (5%) and solubilized in Tween 20 by gavage on day 8 of pregnancy. The low-, mid-, and high-dose group contained 6, 9, and 14 animals. The doses were chosen based on the median effective dose of retinoids that induce terata (ED₅₀) in hamsters. Animals were sacrificed on day 14 and average fetal and maternal body weights were measured. Developmental parameters monitored included number of litters, abnormal litters, implantation sites, number resorptions, number of abnormal live fetuses, number dead fetuses, mean litter frequency, and characterization of malformations. The only malformation recorded was that one fetus at the 480 mg/kg bw dose level exhibited one hind limb lateral rotation. The authors reported concluded that this effect was not associated with administration of the test substance. The authors concluded that dose levels up to and including 480 mg/kg bw of *beta*-ionone failed to show any evidence of maternal or developmental toxicity in golden Syrian hamsters [Willhite, 1986]. In the same study, dose levels of 96 or 960 mg/kg bw of psuedoionone (a structurally related ketone) were given to golden Syrian hamsters on day 8 of pregnancy. The only effect reported was a significant reduction in maternal weight gain in the 960 mg/kg bw group. There were no developmental effects at either dose level [Willhite, 1986].

3.5.3 New Testing Required

None.

3.6 Test Plan Table

Chemical	Chemical and Physical Properties				
	Melting Point	Boiling Point	Vapor Pressure	n-Octanol/Partition Coefficient	Water Solubility
CAS No. 127-51-5 <i>alpha</i> -iso-Methylionone	Calc	A, Calc	A, Calc	A, Calc	A, Calc
CAS No. 1335-46-2 Methyl ionone (mixture of isomers)	Calc	A, Calc	A, Calc	R, Calc	A

Chemical	Environmental Fate and Pathways			
	Photodegradation	Stability in Water	Biodegradation	Fugacity
CAS No. 127-51-5 <i>alpha</i> -iso-Methylionone	Calc	Calc	A	Calc
CAS No. 1335-46-2 Methyl ionone (mixture of isomers)	R	NA	A, R	Calc

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Acute Toxicity to Aquatic Plants
CAS No. 127-51-5 <i>alpha</i> -iso-Methylionone	A, Calc	Test, Calc	Test, Calc
CAS No. 1335-46-2 Methyl ionone (mixture of isomers)	R, Calc	Calc	Calc

Chemical	Human Health Toxicity					
	Acute Toxicity	Genetic Toxicity <i>In Vitro</i>	Genetic Toxicity <i>In Vivo</i>	Repeat Dose Toxicity	Reproductive Toxicity	Developmental Toxicity
CAS No. 127-51-5 <i>alpha-iso-Methylionone</i>	A	A	R	A	R	R
CAS No. 1335-46-2 Methyl ionone (mixture of isomers)	A	A	A	A, R	R	R

Legend	
Symbol	Description
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

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The Flavor and Fragrance High Production Volume Consortia

The Terpene Consortium

Robust Summaries For Ionone Derivatives

Methyl ionone (mixture of isomers)

CAS No. 1335-46-2

alpha-iso-Methylionone

CAS No. 127-51-5

FFHPVC Terpene Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:
The Flavor and Fragrance High Production Volume Chemical Consortia
1620 I Street, NW, Suite 925
Washington, DC 20006
Phone: 202-331-2325
Fax: 202-463-8998

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The Flavor and Fragrance High Production Volume Consortia

Robust Summaries for Ionone Derivatives

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al.*, 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 Chemical and Physical Properties

1.1 Melting Point

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for substance	Calculated
Method/guideline	Mean or Weighted
Melting Point	45.26 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency
Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for substance	Calculated
Method/guideline	Mean or Weighted

Melting Point	59.38°C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

1.2 Boiling Point

Substance Name	Methyl ionone (mixture of <i>isomers</i>)
CAS No.	1335-46-2
Method/guideline	Measured
Boiling Point	266.2 °C
Pressure	1013 mb
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Hoffmann-LaRoche, Inc. (2000) Isoraldeine 70 Safety Data Sheet. Red Corner Report, No. B-108,080 vom 17.6., 1983, Kradolfer (Nr. 95931). Unpublished report.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Measured
Boiling Point	238 C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction..
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	Methyl ionone (mixture of <i>isomers</i>)
CAS No.	1335-46-2
Method/guideline	Measured
Boiling Point	238 C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	<i>alpha-iso</i> -Methylionone
-----------------------	--------------------------------

CAS No.	127-51-5
Method/guideline	Calculated /Adapted Stein & Brown method
Boiling Point	271.6 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Calculated /Adapted Stein & Brown method
Boiling Point	274.6 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

1.3 Vapor Pressure

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Measured
Vapor Pressure	0.006 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Measured

Vapor Pressure	0.005 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Fragrance Materials Association (FMA)

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated/modified Grain method
Vapor Pressure	0.00127 mm Hg
Temperature	25 °C
Remarks for Test Conditions	Experimental boiling point used 266.2 C.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

Substance Name	Methylionone
CAS No.	1335-46-2
Method/guideline	Calculated/modified Grain method
Vapor Pressure	0.0093 mm Hg
Temperature	25 °C
Remarks for Test Conditions	Experimental boiling point used 266.2 C.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPWIN EPI Suite (2000) US Environmental Protection Agency

1.4 n-Octanol/Water Partition Coefficient

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for Substance	Main isomer, <i>alpha-iso</i> -methylionone, 87.8%
Method/guideline	Measured/OECD No.117; reverse phase high performance liquid chromatographic method
GLP	Yes
Year	1994
Log Pow	4.6
Temperature	24 °C
Remarks for Test Conditions	The test substances and seven substances of log Pow (calibration solution) are subjected to HPLC (HP 1050) with a UV-visible detector at 24 °C. Following calibration, the HPLC of test solutions are chromatographed followed by the calibration solution again. Measured retention times are used to determine log Pow.
Conclusion Remarks	The log Pow of <i>alpha-iso</i> -methylionone is determined to be 4.6 at 24 °C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Rudio J. (1994a) Partition coefficient n-octanol/water of Isoraldeine according to OECD Guideline No. 117. Study No. 94-E70. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue <i>beta</i> ionone, 97%
Method/guideline	Measured/OECD No.117; reverse phase high performance liquid chromatographic method
GLP	Yes
Year	1994
Log Pow	4.1
Temperature	24 °C
Remarks for Test Conditions	The test substances and seven substances of log Pow (calibration solution) are subjected to HPLC (HP 1050) with a UV-visible detector at 24 °C. Following calibration, the HPLC of test solutions are chromatographed followed by the calibration

Conclusion Remarks	solution again. Measured retention times are used to determine log Pow. The log Pow of <i>beta</i> -ionone is determined to be 4.1 at 24 °C.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Rudio J. (1994b) Partition coefficient n-octanol/water of ionone, <i>beta</i> synt according to OECD Guideline No. 117. Study No. 94-E68. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Measured/OECD No. 117
GLP	Yes
Year	1994
Log Pow	4.6
Temperature	24 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Givaudan-Roure Inc. (1994) Partition Coefficient n-octanol/water of methyl ionone. Unpublished report.

Substance Name	<i>alpha</i> -iso-Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Log Pow	4.84
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U S Environmental Protection Agency

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Calculated
Log Pow	4.84

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U S Environmental Protection Agency

1.5 Water Solubility

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Measured
GLP	Yes
Year	1991
Value (mg/L) at Temperature	16 mg/L at 20 °C
Remarks for Test Conditions	The solubility of the test substances was determined according to the OECD Guidelines for Testing Chemicals No. 105, 'Water Solubility' (flask method)
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Schlienger C. (1992b) 96-Hour acute toxicity study with Isoraldein 70 in rainbow trout. Report No. B-161751. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Measured for <i>gamma</i> methyl ionone
Value (mg/L) at Temperature	0.009 % W/V (90 mg/L)
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Bush, Boake, Allen, Inc. (BBA) (1990) Biodegradability of p-t-butyl- <i>alpha</i> -methylhydrocinnamic aldehyde and methyl- <i>alpha</i> -ionone. Unpublished report.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5

Method/guideline	Calculated
Value (mg/L) at Temperature	4.8 mg/L at 25 °C
Remarks for Test Conditions	Log Kow used: 4.6 (measured)
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN 2000 US Environmental Protection Agency

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2.1 Photodegradation

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Test Type	AOPWIN
Half-life t_{1/2}	0.752 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency

2.2 Stability in Water

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method	Bond SAR method
Test Type	Calculated
Remarks Results	Half-life: river 8 .655 hours; lake 168.9 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency

2.3 Biodegradation

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for Substance	Mixture of 55% <i>alpha-iso</i> -methylionone and 28% <i>alpha</i> -methylionone
Method	Sealed vessel test (based on OECD 301B)
Test Type	CO2 production test
GLP	No
Year	1992
Contact Time	56 days
Innoculum	Unacclimatized activated sludge
Remarks for Test Conditions	The test material (10 mg DOC/L) and secondary effluent from an unacclimatized activated sludge were shaken in a sealed vessel at 14-22 °C for 56 days. The headspace carbon dioxide level and inorganic carbon in the test medium was analyzed.
Degradation % After Time	61.8% after 28 days
10 day Window Criteria	No
Total degradation	60% pass level after 28 days
Remarks Results	Test intended to monitor inherent and ultimate biodegradability using test protocol (301B) used to measure ready biodegradability in 28 days. Test suitable for analysis of volatile substances
Conclusion Remarks	The test substance was considered as inherently biodegradable under modified ready test conditions.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	King J. M. (1992) The inherent biodegradability of base perfumes in the sealed vessel test. BD/PER/15. Unpublished report.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for Substance	Mixture of isomers composed of 60-70% <i>alpha iso</i> -methylionone, 17-30% <i>beta-iso</i> -methylionone, <i>alpha</i> - and <i>beta</i> -methylionone, 91.4% pure: Isoraldein 70
Method/guideline	Modified MITI Test (II)/OECD 302C

Test Type	Inherent Biodegradability: Modified MITI Test (II), 5/1981
GLP	Yes
Year	1992
Contact Time	28 days
Innoculum	Mixture (1:1) from city sewage plant and chemical sewage plant
Remarks for Test Conditions	The test substance (30 mg/L) or reference substances (100 mg/L) sodium benzoate was inoculated with a mixture of activated sludge (100 mg dry sludge/L) in a closed oxygen consumption measuring device for 28 days at 25 °C. Oxygen concentration was monitored continuously using a BOD meter. Percent biodegradation values were arithmetic mean of 2 or 3 independent measurements.
Degradation % After Time	63.4% after 56 days
Results	Negative degradation values were recorded from days 1 to 7 for the test substances. Maximum degradation rate was 3.5%/day at days 9-12 and was reduced to 0.9% at day 19. The reference substance was 100% degraded after 28 days.
10 day Window Criteria	No
Time Required for 10% Degradation	12 days
Classification	Isoraldeine gave evidence of inherent, primary biodegradation and was slightly toxic to microorganisms
Conclusion Remarks	A mixture of methylionones containing 60-70% <i>alpha</i> -isomethylionone shows evidence of inherent, primary biodegradability in an MITI II Test. It was slightly toxic for activated sludge microorganisms.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Schlienger C. (1992a) Inherent biodegradability: Modified MITI-TEST (II) for Isoraldein 70. GLP Test No. PSU 92/2-MII. Unpublished Report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Mixture of isomers composed of 55-65% <i>alpha</i> -isomethylionone, 22-32% <i>alpha</i> -methylionone, 1-5% <i>beta</i> -methylionone, and 4-8% <i>beta</i> -isomethylionone, 1-5% of <i>beta</i> or <i>gamma</i> -methylionone, 98%, sum of isomers
Method/guideline	Biodegradability test
Test Type	Method F, Assessment of biodegradability, 1981
GLP	No
Year	1990

Contact Time	31 days
Innoculum	Buffered solution of activated sludge
Remarks for Test Conditions	Methylionone mixture was mixed with a buffered solution of 30 mg activated sludge/L. The concentration of the test material was calculated to be 50 mg DOC/L. The solution was stirred under fully aerobic conditions in the dark at 20 °C for 28 days. A hard standard of orthophenyldiamine (51 mg DOC/L) was run at the same time
Degradation % After Time	99.1% at day 31
Results	The test material was 95.7% degraded at day 1 and 99.1% at day 31. The hard standard was 12% biodegraded after 14 days
Time required for 10% degradation	Less than 1 day
Total degradation	Yes
Classification	Completely biodegradable
10 day window criteria	Yes
Conclusion Remarks	The mixture of methylionone isomers was completely biodegradable within 28 days
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
Reference	Stickley D. P. (1990) Biodegradability of Lilestrialis and gamma-methylionone 600 UC. Report No. 8720. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Mixture of isomers composed of 60-70% <i>alpha iso</i> -methylionone, 17-30% <i>alpha</i> -methylionone, 0-8% <i>beta</i> -methylionone, and 0-8% <i>beta</i> -isomethylionone, 97.6%, sum of isomers
Method/guideline	MITI Test/OECD 301C
Test Type	Ready Biodegradability Test
GLP	Yes
Year	1990
Contact Time	28 days
Innoculum	Mixture of sludge from city sewage plant (Geneva) and chemical sewage plant (Vernier-ouest, Geneva)
Remarks for Test Conditions	Initial test concentrations: activated sludge, 30 mg/L; Test substance, 107 mg/L; Reference substances, aniline, 93 mg/L. Temperature maintained at 20 °C in a closed system oxygen consumption apparatus.
Degradation % After Time	70.5%

Results	Ionone mixture is biodegradable after 28 days
Time required for 10% degradation	5 days
10 day Window Criteria	Yes
Total degradation	70.5%
Classification	60% pass level exceeded after 28 days
Remarks Results	Reference substance achieved maximum biodegradability within 15 days
Conclusion Remarks	Methylionone (mixture of isomers) is readily biodegradable after 28 days
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Calame R. and Ronchi W. (1990) Isoraldeine 70. Determination of ready biodegradability. Report No. 90-42/B. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>beta</i> -ionone, synthetic
Method/guideline	Respirometric method
Test Type	Biodegradability test
GLP	No
Year	1991
Contact Time	28 days
Innoculum	Activated sludge
Remarks for Test Conditions	In a basic culture medium, 100 mg/L of test material or 100 mg/L of reference substance (aniline) and 30 mg/L activated sludge and oxygen concentration was measured at daily intervals over 28 days.
Degradation % After Time	80% after 28 days
10 day window criteria	Yes
Time required for 10% degradation	5 days
Remarks for Results	<i>Beta</i> -ionone was 80% biodegraded over 28 days and the reference substance was 89% degraded over 28 days
Conclusion Remarks	<i>beta</i> ionone underwent ready biodegradation over 28 days in a respirometric test
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Givaudan-Roure Inc. (1991) Biodegradability test of ionone, beta, and synthetic. Report No. 5992503. Unpublished report.

2.4 Fugacity

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Air
Estimated Distribution and Media Concentration	7.77%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Water

Estimated Distribution and Media Concentration	2.49%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Soil
Estimated Distribution and Media Concentration	87.7%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I

Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Sediment
Estimated Distribution and Media Concentration	1.95%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylnone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	1.061%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylnone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model

Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Fish
Estimated Distribution and Media Concentration	0.0050%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Aerosol
Estimated Distribution and Media Concentration	0.000088%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5

Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Air-Water Partition Coefficient
Absorption coefficient	0.0062
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylnone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Soil-Water Partition Coefficient
Absorption coefficient	783
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-580-56-8
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Sediment-Water Partition Coefficient
Absorption coefficient	1570
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Suspended Sediment-Water Partition Coefficient
Absorption coefficient	4900
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental

models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Fish-Water Partition Coefficient
Absorption coefficient	1990
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Use d	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, calculated MP & VP
Media	Aerosol-Air Partition Coefficient
Absorption coefficient	564000
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or

metabolism.

References

Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press. Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Air-Water Partition Coefficient
Absorption coefficient	0.137
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Soil-Water Partition Coefficient
Estimated Distribution and Media Concentration	1390

Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Sediment-Water Partition Coefficient
Absorption coefficient	2790
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow

Media	Suspended Sediment-Water Partition Coefficient
Absorption coefficient	8710
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Fish-Water Partition Coefficient
Absorption coefficient	3540
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay

Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Aerosol-Air Partition Coefficient
Absorption coefficient	559000
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Air
Estimated Distribution and Media Concentration	51.3%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.

Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log
Media	Water
Estimated Distribution and Media Concentration	0.747%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Soil
Estimated Distribution and Media Concentration	46.9%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.
Substance Name	Methyl ionone (mixture of isomers)

CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Sediment
Estimated Distribution and Media Concentration	1.04%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.033%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Fish
Estimated Distribution and Media Concentration	0.0026%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Model Conditions	25 °C, 100,000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	Calculated MW, water solubility, MP, VP, log Kow
Media	Aerosol
Estimated Distribution and Media Concentration	0.00057%
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism.

References

Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publishing, CRC Press, Boca Raton, FL.

3 Ecotoxicity

3.1 Acute Toxicity to Fish

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for Substance	Mixture of isomers composed of 60-70% <i>alpha</i> isomethylionone, 17-30% <i>beta-iso</i> -methylionone, <i>alpha</i> - and <i>beta</i> -methylionone, 91.4% pure
Method/guideline	Fish acute toxicity test/OECD 203
Test Type	Experimental
GLP	Yes
Year	1992
Species/Strain/Supplier	Rainbow trout (<i>Oncorhynchus mykiss</i>)
Exposure Period	96 hour
Remarks for Test Conditions	Rainbow Trout (average length, 5.8 cm), acclimatized for 12 days, were exposed to a series of 5 test concentrations of 0, 7.8, 10.9, 15.3, 21.4, or 30 mg/L dispersed in Polysorbate 80 (10 mg/L) for 96 hours at 17.1 °C. Control fish were exposed to Polysorbate 80 (10 mg/L). Fish were observed twice daily for mortality and symptoms. pH values and water temperature were monitored after substance addition at 24 hour intervals. Dissolved oxygen was measured at the beginning of the experiment and at 96 hours.
Observations on precipitation	No precipitation
Nominal concentrations as mg/L	0, 7.8, 10.9, 15.3, 21.4, and 30 mg/L test material in 10 mg/L Polysorbate 80 dispersant.
Remarks fields for results	Mortality at 96 hours: 0/10 at 0 mg/L (10 mg/L Polysorbate 80); 0/10 at 7.8 mg/L (7.8 mg/L Polysorbate 80); 8/10 at 10.9 mg/L (10 mg/L Polysorbate 80); 10/10 at 15.3 mg/L and higher (10 mg/L Polysorbate 80). pH values, 8.0-8.9; dissolved oxygen 9.0-9.7 mg/L; water temperature, 17 °C. LD0 = 7.8 mg/L and LD100 = 15.3 mg/L
Conclusion Remarks	LC50 = 10.9 mg/L from linear least square regression line obtained from plot of log concentration versus % mortality data
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Schlienger C. (1992b) 96-Hour acute toxicity study with isoraldein 70 (Ro 01-8915/000) in rainbow trout. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>beta</i> -ionone
Method/guideline	Fish acute toxicity test
Test Type	Experimental
GLP	No
Year	1989
Species/Strain/Supplier	Rainbow trout (<i>Oncorhynchus mykiss</i>)
Exposure Period	48 hour
Remarks for Test Conditions	Rainbow Trout (length, 6-8 cm) were exposed to 0, 5, and 10 mg/L <i>beta</i> -ionone for 48 hours at 16+/-1 °C.
Observations on precipitation	Not reported
Nominal concentrations as mg/L	0, 5, or 10 mg/L
Remarks for Results	Mortality at 48 hours: 0/10 at 0 mg/L; 0/10 at 5 mg/L; 10/10 at 10 mg/L
Conclusion Remarks	LC0 = 5 mg/L and LC100 = 10 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 3. Does not meet important criteria of current standard methods, but results are consistent with current results obtained by current OECD guideline study
Reference	Grothe J. (1989) Ecotoxicity attachment for <i>beta</i> -ionone. Roche report No. E-29/89. Unpublished report.

Substance Name	<i>alpha</i> -iso-Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	14 day
Remarks for Results	Neutral organic SAR
Conclusion Remarks	LC50 = 0.931 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Remarks for Substance	CLOGP
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Conclusion Remarks	Vinyl/allyl ketones: LC50 = 2.04 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency..

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for Substance	SRC
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Conclusion Remarks	Vinyl/Allyl ketones: LC50 = 2.88 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Conclusion Remarks	Vinyl/allyl ketones: LC50 = 0.296 mg/L

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	<i>Daphnia magna</i>
Remarks for Test Conditions	CLOGP
Exposure period	48 hours
EC50, EL50, LC0, at 24,48 hours	Vinyl/allyl ketones: LC50 = 0.597 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	<i>Daphnia magna</i>
Remarks for Test Conditions	SRC
Exposure period	48 hours
EC50, EL50, LC0, at 24,48 hours	Vinyl/allyl ketones: LC50 = 0.672 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.3 Acute Toxicity to Aquatic Plants

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Remarks for Substance	CLOGP
Conclusion Remarks	Vinyl/allyl ketones: EC50 = 0.266 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Remarks for Substance	SRC
Conclusion Remarks	Vinyl/allyl ketones: EC50 = 0.332 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

4 Human Health Toxicity

4.1 Acute Toxicity

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1967
Species/strain	Mouse/CF-1
Sex	Male and Female
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	CF-1 mice of both sexes were orally administered the compound. LD50 was calculated by the method of Miller and Tainter (Proc. Soc. Exptl. Biol. Med. 57:261, 1944)
Value LD50 or LC50 with confidence limits	LD50 = 8714 (95% C.I., +/- 252 mg/kg)
Number of deaths at each dose level	
Remarks for Results	
Conclusion Remarks	The oral LD50 was calculated to be LD50 = 8714 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffmann-LaRoche, Inc. (1967) Acute toxicity, eye and skin irritation test on aromatic compounds. Unpublished report.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Method/guideline	Not given
Test Type	Acute oral toxicity

GLP	Ambiguous
Year	1973
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The oral LD50 of <i>alpha-iso-methylionone</i> was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1973a) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	<i>alpha-iso-Methylionone</i>
CAS No.	127-51-5
Remarks for Substance	<i>alpha-iso-methylionone</i> (pseudo product)
Method/guideline	Not given
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Dose tested: 5900 mg/kg
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	1/10 at 5000 mg/kg

Conclusion Remarks	The oral LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1977b) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>alpha</i> -ionone
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1967
Species/strain	Mouse/CF-1
Sex	Male and Female
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	CF-1 mice of both sexes were orally administered the compound. LD50 was calculated by the method of Miller and Tainter. (Proc. Soc. Exptl. Biol. Med. 57:261, 1944)
Value LD50 or LC50 with confidence limits	LD50 = 6657 mg/kg (95% C.I., +/- 652 mg/kg)
Conclusion Remarks	The oral LD50 was calculated to be 6650 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffmann-LaRoche, Inc. (1967) Acute toxicity, eye and skin irritation test on aromatic compounds. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>beta</i> -ionone
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute oral toxicity

GLP	Ambiguous
Year	1967
Species/strain	Mouse/CFW
Sex	Male
# of animals per sex per dose	5
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Male CFW-mice were orally administered the compound. Five mice were used per dose level and were observed 72 hours for mortality. LD50 was calculated by the Method of Miller and Tainter (Proc. Soc. Exptl. Biol. Med. 57:261, 1944.
Value LD50 or LC50 with confidence limits	LD50 = 5331 mg/kg (95% C.I., +/- 755 mg/kg)
Conclusion Remarks	The oral LD50 was calculated to be 5331 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Hoffmann-LaRoche, Inc. (1967) Acute toxicity, eye and skin irritation test on aromatic compounds. Unpublished report.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl Ionone (Gamma type)
Method/guideline	Not given
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1973
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Observations for mortality and/or systemic effects were made over a 14-day period. 5000 mg/kg of test substance was administered to the animals.

Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The oral LD50 was shown to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Data Reliabilities Remarks	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1973b) Acute toxicity studies on rats and rabbits. Unpublished Report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl ionone (mixture of isomers: methyl- <i>alpha</i> ionone, <i>alpha</i> - <i>iso</i> -ionone, methyl- <i>beta</i> -ionone, pseudo product)
Method/guideline	Not given
Test Type	Acute oral toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Dose tested: 5000 mg/kg.
Value LD50 or LC50 with confidence limits	Oral LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The oral LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1977a) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.
Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2

Remarks for Substance	Data for homologue, <i>beta</i> -Ionone
Method/guideline	Not given
Test Type	Acute intraperitoneal toxicity
GLP	Ambiguous
Year	1965
Species/strain	Mouse
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Intraperitoneal
Vehicle	None
Value LD50 or LC50 with confidence limits	LD50 = 2277 mg/kg
Conclusion Remarks	The intraperitoneal LD50 was calculated to be 2277 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Sporn A., Schobeschm O., Marin, V., Pansitescu, E. and Runcan, L. (1965) The Toxicity of Butyl Acetate, Methyl Naphtyl Ketone and Ionone. Igiena, XII(5), 437-446.

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Remarks for Substance	<i>alpha-iso</i> -methylionone (pseudo product)
Method/guideline	Not given
Test Type	Acute dermal toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Dermal
Remarks for Test Conditions	Doses tested: 2500 and 5000 mg/kg.

Value LD50 or LC50 with confidence limits	Dermal LD50 greater than 5000 mg/kg
Number of deaths at each dose level	6/10 at 5000 mg/kg
Remarks for results	Diarrhea in 2, anorexia and lethargy in 1 at 5000 mg/kg, moderate to severe redness in 4 animals and severe edema in rabbits treated with 2500 mg/kg; severe redness and moderate edema in rabbits treated with 5000 mg/kg.
Conclusion Remarks	The dermal LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1977b) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl ionone (mixture of isomers: methyl- <i>alpha</i> ionone, <i>alpha</i> - <i>iso</i> -ionone, methyl- <i>beta</i> -ionone, pseudo product)
Method/guideline	Not given
Test Type	Acute dermal toxicity
GLP	Ambiguous
Year	1977
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Dermal
Remarks for Test Conditions	Dose tested: 5000 mg/kg
Value LD50 or LC50 with confidence limits	Dermal LD50 > 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Remarks for results	Slight lethargy, ataxia, discharge from nose & mouth, negative righting reflex in 1; severe skin irritation in all animals with moderate to severe edema.
Conclusion Remarks	The dermal LD50 was calculated to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Data Reliabilities Remarks	Code 2. Basic data given: comparable to guidelines/standards.

References

Moreno O. M. (1977a) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Methyl Ionone (Gamma type)
Method/guideline	Not given
Test Type	Acute dermal toxicity
GLP	Ambiguous
Year	1973
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	8
Vehicle	None
Route of Administration	Dermal
Remarks for Test Conditions	5000 mg/kg of the test substance was applied to abraded rabbit skin.
Value LD50 or LC50 with confidence limits	Dermal LD50 greater than 5000 mg/kg
Number of deaths at each dose level	0/10 at 5000 mg/kg
Conclusion Remarks	The dermal LD50 was shown to be greater than 5000 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1973b) Acute toxicity studies on rats and rabbits. Unpublished report to RIFM.

4.2 Genetic Toxicity

4.2.1 In vitro Genotoxicity

Substance Name	<i>alpha-iso</i> -Methylionone
CAS No.	127-51-5
Method/guideline	Ames
Test Type	Reverse mutation

System of Testing	Bacterial
GLP	No
Year	1983
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	Up to 3600 ug/plate
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Remarks for Test Conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo(a)pyrene.
Results	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. <i>Fd. Chem. Toxic.</i> 21(6), 707-719.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data on <i>beta</i> ionone, 98% pure
Method/guideline	Ames
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1986
Species/Strain	<i>Salmonella typhimurium</i> TA 100, TA98, TA97, TA1535, and TA1537
Metabolic Activation	Male Sprague Dawley rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	1-180 ug per plate

Statistical Methods	Not given
Remarks for Test Conditions	After 48-hour incubation at 37 C, each assay plate was counted. Routine positive control plates were prepared: sodium azide for TA1535 and TA100, 4-nitro-o-phenylenediamine for TA98, and 9-aminoacridine for TA97 and TA1537, 2-aminoanthracen.
Results	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Mortelmans K., Haworth, S., Lawlor, T., Speck, W., Tainer, B and Zeiger, E. (1986) Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. Environmental Mutagenesis, 8(Supp. 7), 1-119.

Substance Name	Methyl ionone (mixture of <i>isomers</i>)
CAS No.	1335-46-2
Remarks for Substance	Data for delta methylionone
Method/guideline	Ames
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1983
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	Up to 3600 ug/plate
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Remarks for Test Conditions	Positive controls were run in each experiment with the reference mutagens sodium azide and benzo(a)pyrene
Results	No mutagenic effects
Cytotoxic concentration	Not given

Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of Artificial Flavouring Substances for Mutagenicity in the Salmonella/Microsome, BASC and Micronucleus Tests. <i>Fd. Chem. Toxic.</i> 21(6), 707-719.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>alpha</i> -ionone
Method/guideline	Ames
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1982
Species/Strain	<i>Salmonella typhimurium</i> TA98 or TA100
Metabolic Activation	With and without rat liver microsome fraction S9
Remarks for Test Conditions	Negative
Results	No mutagenic effects
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Conclusion Remarks	No evidence of mutagenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Kasamaki A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T. and Urasawa, S. (1982) Genotoxicity of Flavoring Agents. <i>Mutation Research</i> , 105, 387-392.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Method/guideline	Ames (plate incorporation method)
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	Yes
Year	1999
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	Up to 5000 ug/plate
Remarks for Test Conditions	A preliminary toxicity study was performed in the first phase and a mutagenicity assay in the second phase. Test article was dissolved in DMSO and tested at up to 5000 ug/plate. No precipitate was observed up to 5000 ug/plate.
Results	In mutagenicity study, no evidence of mutagenicity or precipitation at concentrations up to and including 5000 ug/plate.
Cytotoxic concentration	Toxicity observed with TA 100 at 667 ug/plate with and 5000 ug/plate without S9 activation. In TA 1535 and TA1537, toxicity observed up to 1000 ug/plate with and up to 3333 ug/plate without metabolic activation.
Genotoxic Effects	No evidence of genotoxicity
Appropriate statistical evaluations?	None given
Remarks for results	In mutagenicity study, no evidence of mutagenicity. Toxicity was observed at concentrations of 1800 ug/plate with TA100 and 1800 ug/plate with TA1537.
Conclusion Remarks	No evidence of mutagenicity at concentrations up to and including 5000 ug/plate.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Wagner V.O. III and Caruthers S.M. (1999) Bacterial Reverse Mutation assay of Methyl Ionone. Unpublished report to RIFM.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for <i>beta</i> ionone isomer
Method/guideline	Ames
Test Type	Reverse mutation

System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	<i>Salmonella typhimurium</i> TA100, TA98, TA1535, and TA1537
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats.
Doses/Concentration	3 umole/plate (600 ug/plate)
Statistical Methods	Method of Kastenbaum and Bowman (1970)
Results	No mutagenicity at 3 umole/plate or 600 ug/plate.
Cytotoxic concentration	Not given
Genotoxic Effects	None
Appropriate statistical evaluations?	None given
Remarks for results	No evidence of precipitation or mutagenicity at 600 ug/plate
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Florin I., Rutberg, L., Curvall, M., and Enzell, C. R. (1980) Screening of Tobacco Smoke Constituents for Mutagenicity Using the Ames' Test. Toxicology, 18, 219-232.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>alpha</i> -ionone
Method/guideline	Chromosomal aberration
Test Type	Chromosomal aberration
System of Testing	Chinese hamster ovary cells
GLP	No
Year	1982
Species/Strain	Chinese hamster
Doses/Concentration	25 mMolar (5150 mg/L or 5150 ug/mL)
Remarks for test conditions	At 25 millimolar (5150 ug/mL), significant increases in chromosome aberrations were found.
Results	Cytogenetic effects at 25 mM
Cytotoxic concentration	Not given

Genotoxic Effects	Increase in chromosomal aberrations
Appropriate statistical evaluations?	None given
Conclusion remarks	Inconclusive results.
Remarks for results	No attempt to monitor cytotoxicity in CHO cells. Limited data presented in article.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Kasamaki, A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T. and Urasawa, S. (1982) Genotoxicity of Flavoring Agents. Mutation Research, 105, 387-392.

4.2.2 In vivo Genotoxicity

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for <i>alpha</i> methylionone
Method/guideline	Sex linked recessive lethal mutation assay (Wuergler et al., 1977)
Test Type	Sex-linked lethal test
GLP	Ambiguous
Year	1983
Species/Strain	<i>Drosophila melanogaster</i>
Sex	Not reported
Route of Administration	Oral-Diet
Doses/Concentration	20mM
Remarks for Test Conditions	Flies were exposed to the test compound prepared in a 5% saccharose solution and 2% ethanol and 2% Tween 80 for compounds with poor water solubility. Further details of the methodology were not reported.
Appropriate statistical evaluations?	Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Remarks for Results	Methylionone did not increase the number of sex-linked recessive lethal mutations as compared to controls.
Conclusion Remarks	Methylionone did not induce sex-linked recessive lethals in <i>Drosophila melanogaster</i> .
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.

References

Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. *Fd. Chem. Toxicol.*, 21(6), 707-719.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for <i>alpha</i> methylionone
Method/guideline	Micronucleus test (Schmid, 1976)
Test Type	Clastogenic assay
GLP	Ambiguous
Year	1983
Species/Strain	Mouse/NMRI
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	825, 1444, or 2063 mg/kg
Remarks for Test Conditions	Groups of 10- to 14-week-old NMRI mice were intraperitoneally injected at 0 and 24 hours with 825, 1444, or 2063 mg/kg bw. At 30 hours, the mice were killed and bone marrow smears were prepared using the staining method of Schmid (1976). Yes. Statistical significance determined by methods of Kastenbaum and Bowman (1970).
Appropriate statistical evaluations?	The mean number of micronucleated PE/1000 PE at 0, 825, 1444, or 2063 mg/kg bw was 1.7, 1.0, 0.7, or 1.9 respectively.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	
Genotoxic effects	None
Conclusion Remarks	Methylionone did not induce micronuclei in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Wild D., King, M.T., Gocke, E. and Eckhardt, K. (1983) Study of artificial flavouring substances for mutagenicity in the salmonella/microsome, basc and micronucleus tests. <i>Fd Chem Toxicol.</i> , 21(6), 707-719.

4.3 Repeat dose Toxicity

Substance Name	<i>alpha-iso</i> -Methylionone
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CAS No.	127-51-5
GLP	Ambiguous
Year	1965
Species/strain	Rat/FDRL
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	3.55 mg/kg for males and 4.10 mg/kg for females
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	Groups of 15 FDRL rats (per sex per dose) were given the a test diet containing the test article diluted in cotton-seed oil (2%) a concentration sufficient to provide the predetermined dosage in 3.55 or 4.10 mg/kg bw for 90 days. Animals were housed individually. Body weights and food and water intake were measured weekly. Hematological examination and blood chemical determinations were performed on 8 rats at week 6 and on all rats at week12. At autopsy, liver and kidney weights were measured. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis.
NOAEL (NOEL)	3.55 mg/kg for male and 4.10 mg/kg for females
Toxic Response/effects by Dose Level	No effects observed
Statistical Evaluation	Student t test
Remarks for Results	Males showed slight but not statistically significant reduced hemoglobin level. There was no change in hematocrit or erythrocyte count. The authors concluded that the effect was within control ranges.
Conclusion Remarks	The administration of 3.55 or 4.10 mg/kg of <i>alpha-iso</i> -methylionone to male and female rats, respectively, resulted in no effects based on any measured parameter.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oser B. L., Carson S. and Oser M. (1965) Toxicological tests on Flavor Matters. Food and Cosmetic Toxicology, 3, 563-569.
Substance Name	Methyl ionone (mixture of <i>isomers</i>)
CAS No.	1335-46-2

Remarks for Substance	Data for homologue, <i>beta</i> -ionone
GLP	Ambiguous
Year	1965
Species/strain	Rat/FDRL
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	11.4 mg/kg for males and 11.6 mg/kg for females
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	Groups of 15 FDRL rats (per sex per dose) were housed individually and given the a test diet containing the test article diluted in cotton-seed oil (2%) a concentration sufficient to provide the predetermined dosage in 3.55 or 4.10 mg/kg bw for 90 days. Animals were housed individually. Body weights and food and water intake were measured weekly. Hematological examination and blood chemical determinations were performed on 8 rats at week 6 and on all rats at week12. At autopsy, liver and kidney weights were measured. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis.
NOAEL (NOEL)	11.4 mg/kg for male and 11.6 mg/kg for females
Toxic Response/effects by Dose Level	No effects observed
Statistical Evaluation	Student t test
Conclusion Remarks	The administration of 11.4 or 11.6 mg/kg of <i>beta</i> -ionone to male and female rats, respectively, resulted in no effects based on any parameter measured.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oser B. L., Carson S. and Oser M. (1965) Toxicological tests on Flavor Matters. Food and Cosmetic Toxicology, 3, 563-569.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>alpha</i> -ionone
GLP	Ambiguous

Year	1965
Species/strain	Rat/FDRL
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	11.8 mg/kg for males and 11.1 mg/kg for females
Exposure Period	90 days
Frequency of Treatment	Continuous
Control Group	Basal diet
Remarks for Test Conditions	Groups of 15 FDRL rats (per sex per dose) were housed individually and given the a test diet containing the test article diluted in cotton-seed oil (2%) a concentration sufficient to provide the predetermined dosage in 3.55 or 4.10 mg/kg bw for 90 days. Animals were housed individually. Body weights and food and water intake were measured weekly. Hematological examination and blood chemical determinations were performed on 8 rats at week 6 and on all rats at week12. At autopsy, liver and kidney weights were measured. Histological examination was performed on the adrenal, bladder, brain, bone marrow, heart, ileum, kidney, liver, lung, lymph nodes, mammary, salivary glands, ovary, pancreas, pituitary, thyroid, large intestines, spinal cord, spleen, stomach and testis.
NOAEL (NOEL)	11.8 mg/kg for males and 11.1 mg/kg for females
Toxic Response/effects by Dose Level	No effects observed
Statistical Evaluation	Student t test
Conclusion Remarks	The administration of 11.8 or 11.1 mg/kg of <i>alpha</i> -ionone to male and female rats, respectively, resulted in no effects based on any parameter measured.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oser B. L., Carson S. and Oser M. (1965) Toxicological tests on Flavor Matters. Food and Cosmetic Toxicology, 3, 563-569.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>alpha</i> -ionone
GLP	Yes
Year	1983
Species/strain	Rat/Sprague-Dawley

Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	10 or 100 mg/kg
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	<p>Groups of Sprague-Dawley rats (15/sex/group) housed in groups of 3 by sex were maintained on diets calculated to result in a daily intake of 10 or 100 mg/kg bw. Body weights and food and water intake were measured every 3rd or 4th day of the study. Hematological examination was performed on rats during weeks 6 and 13 of the study. Blood chemical determinations and urinalysis were performed on weeks 5 and 12. At necropsy, organ weights (brain, liver, spleen, kidneys, caecum, adrenals and gonads (males)) were measured.</p> <p>Histopathological examination of a wide variety of tissues (adrenal, aorta, bladder, brain, caecum, colon, diaphragm, duodenum, epididymis, eye, harderian gland, heart, ileum, kidney, liver, lung, lymph nodes, mammary, muscle, esophagus, ovary, pancreas, pituitary, prostate, rectum, seminal vesicles, skin, spinal cord, spleen, stomach and testis) were performed for the controls and high dose groups. The liver of the low dose group was also subjected to histopathological examination.</p>
NOAEL (NOEL)	10 mg/kg
LOAEL (LOEL)	100 mg/kg
Toxic Response/effects by Dose Level	<p>The intake of <i>alpha</i>-ionone was determined to be 11mg/kg bw for males and females at the low dose and 106-108 mg/kg bw at the high dose. Food intake of the high dose group of males and females were significantly lower than controls. A decrease in neutrophils and lymphocytes were reported in males at the high dose levels at week 6 but not at week 13. At the high dose, lower alkaline phosphatase in males and lower glucose levels in females was reported. The relative kidney weights were statistically significantly greater in males at the high dose. Relative and absolute mean liver weights were statistically increased in males at the high dose. The histological finding was desquamation of the thyroid in females at the high dose.</p>
Statistical evaluations	Student t test (white cell counts) and Fisher exact test (histopathological findings)
Conclusion Remarks	The NOEL for <i>alpha</i> -ionone was shown to be 10 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Gaunt I. F., Butler, W., Ford, G. (1983) The short-term (90 Days) toxicity of <i>alpha</i> and <i>beta</i> -ionones in rats. Unpublished report to IOFI.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>beta</i> -ionone
GLP	Yes
Year	1983
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	10 or 100 mg/kg
Exposure Period	90 days
Frequency of Treatment	Continuous in the diet
Control Group	Basal diet
Remarks for Test Conditions	Groups of Sprague-Dawley rats (15/sex/group) housed in groups of 3 by sex were maintained on diets calculated to result in a daily intake of 10 or 100 mg/kg bw. Body weights and food and water intake were measured every 3rd or 4th day of the study. Hematological examination was performed on rats during weeks 6 and 13 of the study. Blood chemical determinations and urinalysis were performed on weeks 5 and 12. At necropsy, organ weights (brain, liver, spleen, kidneys, caecum, adrenals and gonads (males)) were measured. Histopathological examination of a wide variety of tissues; adrenal, aorta, bladder, brain, caecum, colon, diaphragm, duodenum, epididymis, eye, harderian gland, heart, ileum, kidney, liver, lung, lymph nodes, mammary, muscle, esophagus, ovary, pancreas, pituitary, prostate, rectum, seminal vesicles, skin, spinal cord, spleen, stomach and testis were performed for the controls and high dose groups. The liver of the low dose group was also subjected to histopathological examination.
NOAEL (NOEL)	10 mg/kg
LOAEL (LOEL)	100 mg/kg
Toxic Response/effects by Dose Level	The intake of <i>beta</i> ionone was determined to be 11mg/kg bw for males and females at the low dose and 106-108 mg/kg bw at the high dose. Food intake of the high dose group of males and females were significantly lower than controls. A decrease in erythrocyte counts and hematocrit were reported in males at the high dose levels at week 6 but not at week 13. At the high dose, lower alkaline phosphatase in males and lower glucose levels in females was reported. Relative and absolute mean liver weights were statistically increased in males at the high dose. Relative brain, caecal, liver and kidney weights were

	statistically increased in females at the high dose level.
Statistical Evaluation	Student t test (white cell counts) and Fisher exact test (histopathological findings)
Conclusion Remarks	The NOEL for <i>beta</i> -ionone was shown to be 10 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Gaunt I. F., Butler, W., Ford, G. (1983) The short-term (90 Days) toxicity of <i>alpha</i> and <i>beta</i> -ionones in rats. Unpublished report to IOFI.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, <i>beta</i> -ionone
Method/guideline	The chemopreventive potency of the test material was studied using the DMBA mammary carcinogenesis model.
GLP	No
Year	1995
Species/strain	Rat/Female Sprague-Dawley
Sex	Female
Route of Administration	Oral-Diet
Doses/concentration Levels	36 mmole/kg (approximately 7400 mg/kg)
Exposure Period	24 weeks
Frequency of Treatment	Continuous
Remarks for Test Conditions	Groups of 32 female rats, including a control group, received diet for 24 weeks. Test material was diluted in corn oil and added to the animal food. A single dose of a suspension of DMBA in sesame oil was given at the end of week 2. Observations were survival, body weight and tumor incidence, latency and multiplicity.
Toxic Response/effects by Dose Level	Ionone delayed the incidence of DBMA-induced tumors in female rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Data from study of antitumorigenicity effects of ionone. Limited data collection.
References	Yu S.G., Anderson, P.J. and Elson, C.E. (1995) Efficacy of <i>beta</i> -ionone in the chemoprevention of rat mammary carcinogenesis. Journal of Agricultural and Food Chemistry, 43(8), 2144-2147.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for methylionone isomer, gamma methylionone in phenyl ethyl alcohol
GLP	Yes
Year	1981
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of Administration	Dermal
Doses/concentration Levels	10 mg/kg
Exposure Period	90 days
Frequency of Treatment	Daily
Control Group	Phenethyl alcohol (1 ml/kg)
Remarks for Test Conditions	1% gamma-Methylionone in phenyl ethyl alcohol at a dose of 10 mg/kg was applied topically to the clipped backs of individually housed Sprague-Dawley rats (5/sex/group) daily for 90 days. A control group of 5 male and female rats received 1 ml/kg phenyl ethyl alcohol. Body weights were measured weekly. Hematological examination, clinical chemistry determinations and urinalysis were performed on all animals at termination. At necropsy, liver and kidney weights were measured and histopathological examination was made of the skin, kidneys, liver, sternal bone, and spinal cord.
NOAEL (NOEL)	10 mg/kg
Toxic Response/effects by Dose Level	No toxic effects were observed at 10 mg/kg bw.
Remarks for Results	Based on measurement of body weight gain, hematological examination, blood chemistry determinations, urinalysis, liver and kidney weights and gross and histopathological examination, there was no difference between test and control groups.
Conclusion Remarks	There was no evidence of toxicity induced by treatment with the gamma methyl ionone.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O. M. (1981) 90-Day sub acute dermal toxicity in rats. Unpublished report to RIFM.

4.4 Reproductive Toxicity

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for homologue, ionone
Test Type	Two-generation reproduction
GLP	No
Year	1965
Species/Strain	Rats/White adult
Sex	Male and Female
Route of Administration	Oral-Gavage
Duration of Test	8 months
Doses/Concentration	2 mg/day every other day for 8 months
Premating Exposure period for males	Males treated to same regimen, 2mg/day every other day for 8 months
Premating Exposure period for females	2 mg/day every other day until first reproduction at 24 days
Control Group and Treatment	Controls, 0.1 ml oil vehicle every other day
Remarks for Test Conditions	The influence of the test substance on the reproduction was determined in 48 white rats. The females received during 8 months, 0.1 ml oil solution containing 2 mg test substance every other day. Females were followed through 3 reproduction cycles. Females were monitored for number of pregnancies, average weight, number of born offspring, number of offspring born alive, weight at birth and after 7 and 21 days, and viability of offspring after each reproduction. Females received 24 mg before the first reproduction, 84 mg before the second, and 208 mg before the third reproduction. Offspring from the first reproduction (F1) were allowed to reach maturity. This F1 generation received 15 mg ionone prior to reproduction. The F1 generation was then monitored for the same parameters as monitored above.
NOAEL(NOEL)	1 mg/d (8-10 mg/kg/d)
Actual dose received by dose level and sex	2 mg/day every other day
Parental data and F1 as Appropriate	There were no significant differences between any of the parameters monitored for dams, offspring from three reproductions, or offspring of the F1 generation.
Remarks for Results	An average daily intake of 1 mg/day (2 mg/day every other day) or 8-10 mg/kg/day based on average body weight had no effect on dams or pups in repeated reproductions

Conclusion Remarks	No reproductive effects of 8-10 mg/kg/day of ionone in rats.
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to data collected in guidelines study.
References	Sporn A., Schobeschm O., Marin, V., Pansitescu, E. and Runcan, L. (1965) The toxicity of butyl acetate, methyl naphtyl ketone and ionone. Igiena, XII(5), 437-446.

4.5 Developmental/Teratogenicity Toxicity

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for methylionone homologue, <i>beta</i> ionone, purity > 99% by HPLC
Method/guideline	Experimental/Retinoid Tetratogenicity (Williams, Willhite, 1984)
Test Type	Developmental Toxicity
GLP	No
Year	1986
Species/strain	Hamsters/Golden Syrian
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	14 days (days 1 to 14 of pregnancy)
Doses/concentration Levels	0, 48, 240, or 480 mg/kg
Frequency of Treatment	Single dose on day 8 of pregnancy
Control Group and Treatment	Control group received Tween 20 (0.5 ml/100g)
Remarks for Test Conditions	Timed pregnant LAK:LVG(SYR) hamsters were used. Test material was dissolved in acetone and solubilized in polyoxyethylene sorbitan monolaurate. Final acetone concentration was 5%. Animals received a single dose of test material on day 8 of pregnancy. Fetal and maternal body weights were monitored on day 14. Developmental parameters monitored included number of litters, abnormal litters, implantation sites, number reabsorbed, number abnormal live fetuses, number dead fetuses, mean litter frequency, and characterization of malformations. The median effective Dose for terata and embryonic LD50 were determined.
NOAEL (NOEL) maternal toxicity	480 mg/kg

NOAEL (NOEL)	480 mg/kg
developmental toxicity	
Actual dose received by dose level and sex	48, 240, or 480 mg/kg
Maternal data with dose level	No observations of toxicity at any dose level. No significant change in body weight in dams at any dose levels compared to controls.
Fetal Data with Dose Level	No significant changes in any fetal parameter measured. No malformations at any dose level.
Appropriate statistical evaluations	Fetal and maternal body weight data by Newman-Keuls test; Number of resorptions by Mann-Whitney test, Number abnormal litters by Yates X2 test
Conclusion Remarks	There was no evidence of developmental or maternal toxicity in golden Syrian hamsters given up to 480 mg/kg of <i>beta</i> -ionone by oral gavage.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Willhite C.C (1986) Structure-activity relationships of retinoids in developmental toxicology. II. Influence of the polyene chain of the vitamin A molecule. Toxicology and Applied Pharmacology, 83, 563-575.

Substance Name	Methyl ionone (mixture of isomers)
CAS No.	1335-46-2
Remarks for Substance	Data for methylionone homologue, pseudoionone, purity > 98% by HPLC
Method/guideline	Experimental/Retinoid Tetragenicity (Williams, Willhite, 1984)
Test Type	Developmental Toxicity
GLP	No
Year	1986
Species/strain	Hamsters/Golden Syrian
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	14 days (days 1 to 14 of pregnancy)
Doses/concentration Levels	0, 96, or 960 mg/kg
Frequency of Treatment	Single dose on day 8 of pregnancy
Control Group and Treatment	Control group received Tween 20 (0.5 ml/100g)
Remarks for Test Conditions	Timed pregnant LAK:LVG(SYR) hamsters were used. Test material was dissolved in acetone and solubilized in polyoxyethylene sorbitan monolaurate. Final acetone concentration was 5%. Animals received a single dose of test material on day 8 of pregnancy. Fetal and maternal body

	weights were monitored on day 14. Developmental parameters monitored.
NOAEL (NOEL) maternal toxicity	96 mg/kg
LOAEL(LOEL) maternal toxicity	960 mg/kg
NOAEL (NOEL) developmental toxicity	960 mg/kg
Actual dose received by dose level and sex	96 or 960 mg/kg
Maternal data with dose level	The maternal body weight was significantly depressed following treatment with 960 mg/kg of pseudoionone.
Fetal Data with Dose Level	No significant changes in any fetal parameter measured No malformations at any dose level
Appropriate statistical evaluations	Fetal and maternal body weight data by Newman-Keuls test, Number. of resorptions by Mann-Whitney test, Number abnormal litters by Yates X2 test.
Conclusion Remarks	There was no evidence of developmental toxicity at doses up to an including 960 mg/kg and maternal toxicity at 96 mg/kg in golden Syrian hamsters.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Willhite C.C (1986) Structure-activity relationships of retinoids in developmental toxicology. II. Influence of the polyene chain of the vitamin A molecule. Toxicology and Applied Pharmacology, 83, 563-575.